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Spindle Cell (Kaposiform) Hemangioendothelioma With Kasabach-Merritt Syndrome in an Infant: Successful Treatment With α-2A Interferon

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A two-month-old infant developed a vascular tumor of the right flank which, upon biopsy, proved to be a spindle cell hemangioendothelioma. The increased capillary bed characterizing the neoplasm caused a severe thrombocytopenia together with a consumption coagulopathy (Kasabach-Merritt syndrome). The patient, who was dependent on platelet transfusions, improved quickly after interferon α-2a was given at the dosage of 3.000.000 U/m^2, with resolution of the Kasabach-Merritt syndrome after three weeks and a 75% decrease of the tumor volume within three months of treatment. Med. Pediatr. Oncol. 28:358–361, 1997. © 1997 Wiley-Liss, Inc.

Key words: hemangioendothelioma; Kasabach-Merritt syndrome; interferon α-2a treatment

INTRODUCTION

The term hemangioendothelioma designates a group of vascular tumors intermediate in appearance between hemangioma and angiosarcoma. First described in 1986 as a low-grade angiosarcoma with features of both angiosarcoma and Kaposi's sarcoma [1,2], the spindle cell (Kaposiform) hemangioendothelioma appears to be a previously unrecognized vascular tumor. More recent cases have widened the clinical spectrum of this quite peculiar entity; high-output heart failure secondary to artero-venous fistulas or extensive systemic arterial supply as well as severe thrombocytopenia with evidence of intravascular coagulation (Kasabach-Merritt syndrome) due to large tumors of the trunk, extremities, or abdominal viscera have appeared as life-threatening complications [3,4].

Traditional therapeutic approaches to angiomatous disease, which include surgery, systemic steroids, cryotherapy, laser therapy, radiation therapy, cytotoxic drugs, and selective embolization, are not always successful in the treatment of these soft tissue neoplasms, often displaying locally aggressive behavior or impinging on vital structures.

Interferon α has produced dramatic regressions of childhood angiomatous disease [5,6]. An on-going study at our institution has already accrued 18 evaluable patients, recording a greater than 50% tumor regression in 11/18 patients (paper submitted).

Interferons affect a variety of biological actions; they are potent cytokines displaying complex antiviral, immunomodulating, and antiproliferative effects [7]. In 1980 it was observed that interferons inhibited the motility of cultured endothelial cells [8]; in 1987, interferons were reported to inhibit endothelial cell proliferation [9] and angiogenesis [10] in experimental models. Clinical studies have confirmed the specific angiogenesis inhibitory activity of interferon α not only in childhood hemangiomas, but also in the treatment of other vascular tumors [11].

CASE REPORT

A two-month-old little girl (weight 4.8 kg, length 56 cm, body surface area 0.26 m^2) was admitted to the Department of Plastic Surgery because of a rapidly enlarging vascular tumor of the right flank. The vascular mark, which had made its appearance immediately after birth, had prompted a one-day admission at a primary care center at the age of five days; a ultrasound scan (US) had failed to disclose any soft-tissue abnormality surrounding the small hemangioma.

Upon admission low hemoglobin (7.2 g/dl) and severe thrombocytopenia (16.000/μl) were recorded, as well as a coagulopathy with abnormal partial thromboplastine time (PTT 54 sec., n.v. 29–40 sec.) and a low fibrinogen level (143 mg/dl, n.v. 200–500 mg/dl). Fibrin degrada-

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Fig. 1. CT scan of abdomen at onset (A) and after four months of treatment (B): 75% reduction of tumor volume.

tion products were slightly increased at 30 μg/ml (n.v. < 10 μg/ml). Blood samples for the coagulation panel were obtained from venipunctures or non-heparinized lines. The peripheral smear was remarkable for a decreased platelet number and some red blood cell fragments. Blood chemistry and urinalysis were normal. Thrombocytopenia and consumption coagulopathy were attributed to sequestration and increased destruction of platelets within the hemangioma (Kasabach-Merritt syndrome), while the rapid increase in size of the hemangioma and the accompanying anemia might have been due to hemorrage and microangiopathic hemolysis within the tumor. No bleeding tendency was evident upon clinical examination, except for some petechiae.

Ultrasound scans, computed tomography (CT), and magnetic resonance imaging (MRI) disclosed a tumor of the right adominal wall (6 × 4 × 4 cm on the CT scan) with irregular uptake of contrast mediums, displacing the right kidney and causing a rotation of the vertebral bodies (Fig. 1 a); the vascular supply, as shown by an arteriogram, originated from the right lumbar and intercostal arteries. Because of the rapid increase in size and the aggressive appearance of the tumor open surgical biopsy was performed after packed red blood cell (PRBC) and platelet concentrate (PLT) transfusions.

Histologically the tumor consisted of alternating areas of dilated, thin-walled cavernous vascular spaces and solid areas consisting of relatively bland-appearing spindle cells and epithelioid endothelial cells (Fig. 2), similar to those observed in epithelioid hemangioendothelioma. The spindle cells were frequently lining slit-like vascular channels as those observed in Kaposi's sarcoma. Siderophages were also present. Endothelial cells and, focally, spindle cells, reacted with factor VIII-related antigen. Electron microscopy (not shown) revealed the factor VIII antigen-positive cells to have the ultrastructural features of endothelium, whereas the spindle cells resembled less mature mesenchymal elements.

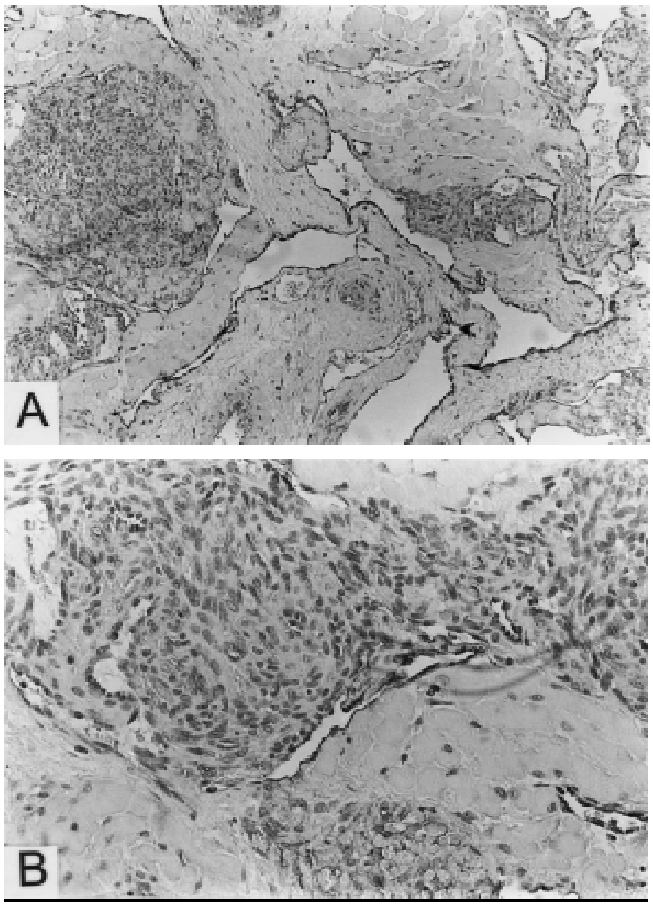

Fig. 2. Spindle cell hemangioendothelioma showing cavernous spaces and cellular spindle areas (HE, 80× (A) and 200× (B)).

After surgery, the little girl was admitted to the intensive care unit; both PRBC and PLT transfusions had to be given on alternate days due to persistently low blood counts (Hb 6.4 g/dl, platelets 11.000/μl), bleeding from the surgical wound, scattered petechiae, and microscopic hematuria. The patient then became part of our on-going study for the treatment of hemangiomas of infants and children with α-2a interferon, after approval by the appropriate institutional review board of Bambino Gesù Children's Hospital in Rome. Informed consent was obtained from the parents. Complete blood counts, coagulation panels, liver function tests and chemistries were performed daily during the first week of treatment, weekly thereafter and monthly after discharge of the patient. Treatment was scheduled for the evening, as this appears to increase the tolerance to the well-known side effects of interferon therapy (flu-like syndrome with chills, mild fever, headache, arthralgyas, and myalgias, usually starting 2–4 hours after injection and lasting 4–8 hours).

Human interferon α-2a (Roferon Roche, specific activity 2×10^8 units/mg of protein) as a sterile solution for subcutaneous injection was obtained from commercial sources. The patient was given 1×10^6 units/m^2 by daily subcutaneous injection; the dose, pending the clinical conditions of the little girl, was rapidly escalated after 3 and 4 days to 2 and then 3×10^6 units/m^2 per day. PLT transfusions were given only in case of clinically significant bleeding. Three weeks after starting interferon therapy the platelet count reached 33.000/μl; after six weeks platelets were 117.000/μl; hemoglobin levels slowly returned to normal and no further PLT or PRBC transfusions had to be given. The only recorded toxicity was a slowly progressing increase in transaminases, reaching a maximum of SGOT (AST) 197 units/L, SGPT (ALT) 250, and γGT (GGTP) 49 IU/l after four months of treatment and slowly decreasing thereafter, returning to normal two weeks after discontinuation of therapy. US scans were performed at close intervals, monitoring tumor size.

The clinical response was striking. A CT scan performed three months after initiating treatment demonstrated a 75% reduction of the product of the two major dimensions of the tumor, which had shrunk to $2 \times 3 \times 2$ cm (Fig. 1b). Interferon therapy was discontinued after six months. A US scan failed to demonstrate any residual tumor eight months after initiating treatment and surgery was not performed at all.

The child is alive and well 36 months from diagnosis and 30 months after completion of treatment; no regrowth of tumor has been observed after withdrawal of interferon.

DISCUSSION

Hemangiomas, the most common tumors of infancy, may affect up to 3% of the pediatric population [11]. The majority of cases pursue a benign course. Cutaneous tumors are seldom fully developed at birth, making their appearance during the first weeks of life. Most lesions, after a phase of rapid growth (proliferative phase) which may last up to 18 months, undergo spontaneous involution. Regression rarely occurs within the first year of life. There is complete resolution of hemangiomas in over 50% of children by the age of 5 years and in over 70% by the age of 7 years, with the remaining tumors completely involuted by age 12 years [13]. While most hemangiomas are small and do not require treatment other than cosmetic repair in some cases, a small percentage may impair vital structures or cause life-threatening complications [14] Mortality in the setting of bleeding from profound thrombocytopenia (Kasabach-Merritt syndrome) in infants with large or extensive hemangiomas is still 30–40% despite therapy [15]. While most hemangiomas of infancy respond to high doses of prednisone [16] only 30% of the ''alarming hemangiomas'' regress after high-dose corticosteroid treatment, with a lower response rate reported in Kasabach-Merritt syndrome [14,

17]; the remaining 70% are either unresponsive, with a significant mortality rate, or require long-term steroid maintenance treatment.

Interferons may interfere with angiogenesis not only by blocking in-vitro endothelial cell motility and proliferation but also by directly inhibiting in-vitro angiogenesis [8–10]. Furthermore, interferons exert direct antiproliferative effects by a cytostatic mechanism that slows the growth of tumor cells by increasing the length of their cell cycle [18]. The improvement observed in patients with consumptive coagulopathies may also be due to decreased platelet adherence and trapping resulting from increased endothelial prostacyclin production and release [19].

The results obtained in the treatment of life-threatening angiomas of infancy [5,6] led to an evaluation in a large hemangioendothelioma.

Because regression of angiomatous disease is rarely observed within the first year of life, it is reasonable to assume that the early and impressive responses observed in our, as well as in the other cases from the literature, were treatment-related.

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